IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF UTAH

CENTRAL DIVISION

UNIVERSITY OF UTAH RESEARCH FOUNDATION, A UTAH NONPROFIT CORPORATION, THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA, A PENNSYLVANIA NONPROFIT CORPORATION; HSC RESEARCH AND DEVELOPMENT LIMITED PARTNERSHIP, A CANADIAN LIMITED PARTNERSHIP ORGANIZED UNDER THE LAWS OF THE PROVINCE OF ONTARIO; ENDORECHERCHE, INC., A CANADIAN CORPORATION ORGANIZED UNDER THE LAWS OF THE PROVINCE OF QUEBEC; AND MYRIAD GENETICS, INC., A DELAWARE CORPORATION,

PLAINTIFFS,

VS.

AMBRY GENETICS CORPORATION,

DEFENDANT.

CASE NO. 2:13-CV-640RJS
2:13-CV-643

SALT LAKE CITY, UTAH

AUGUST 23, 2013

TUTORIAL/MISCELLANEOUS HEARING
BEFORE THE HONORABLE ROBERT J. SHELBY
UNITED STATES DISTRICT COURT JUDGE

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P-R-O-C-E-E-D-I-N-G-S

(1:30 P.M.)

THE COURT: Good afternoon. We'll go on the record in consolidated -- cases are not consolidated, but for purposes of this hearing they are. These are case numbers 2:13-CV-640 and 643, University of Utah Research Foundation and Myriad Genetics and the like versus Ambry Genetics in the 640 case, Gene By Gene in the 643 case.

Counsel, I think we have -- we have plenty of you here today. Why don't we take a moment. I have your names here, but why don't you make your appearances, if you would, please.

MR. MANGUM: Thank you, Your Honor. David Mangum and Kristine Johnson of Parsons Behle for the Plaintiffs. Also with us and Counsel of Record, Ben Jackson, who is Senior Director of Legal Affairs For Myriad Genetics. At counsel table and hiding behind the easel is Dr. Ben Roa. He is the Vice-President of Technology and Development and Senior Lab Director for Myriad. He will be assisting in the technical presentation today.

Your Honor, I would just introduce you to also others that are in the courtroom today, Mr. Richard Marsh, who is Executive Vice-President and General Counsel for Myriad, and Matt Gordon, who is the Director of Intellectual Property for Myriad. Thank you.

THE COURT: Thank you, Mr. Mangum.

Mr. Gaede.

MR. GAEDE: Good afternoon, Your Honor. Good to see you again.

THE COURT: Nice to see you.

MR. GAEDE: Bill Gaede on behalf of the Defendants. I'd like to introduce to Your Honor Dr. David Pribnow Dr. Pribnow has been a leader in the field since 1975 and he may also be here to answer any questions that you have.

Mr. Cataxinos: And Edgar Cataxinos and Joe Walkowski representing Ambry from TraskBritt.

MR. GAEDE: And of course we have Mr. Hatch here in the courtroom as well.

Mr. Hatch: Behind the bar, Your Honor.

THE COURT: Well, good afternoon to all of you, and thank you for making time to visit with us today. We've appreciated receiving your materials. You've all obviously spent some time and effort trying to figure out how best to teach a generalist about the subject matter. We've worked to try to familiarize ourselves generally with some of the information so it won't be totally new to us.

We have received some objections and responses to objections to some of the proposed slides and materials. I've reviewed those. My view is that we ought to take most of those in turn I think and just see what it is you all intend

to say about it. Though I will say I think I'm disinclined to get into a discussion in any way about the claim language of the claims. There are several slides that are just recitations of portions of the claims. I understand that they may be offered to provide some context for some of the scientific terms or technical terms we'll be discussing, but what we're not doing today, of course, is engaging in some preliminary claim construction or anything like that. If there are disagreements about whether there are terms that are used in the science that are terms of art that have specific meanings, then let's see if we can sort that out as best we can, or at least identify what the dispute is and what different scientists think about those terms.

But generally I think what we're here to do today is to try and just provide a background and an educational format for me and my staff so that we can begin to better analyze the issues we'll have to tackle at our injunction hearing where we'll have a chance to argue about what the consequences are of what we'll learn today.

So with that in mind, Mr. Mangum, you are the plaintiff and you have the burden on your motion and I think it makes sense as the patent holder for Myriad -- and I'll just refer to the plaintiffs generally as Myriad and maybe I'll just refer to the defendants as defendants since you are discrete entities. But, Mr. Mangum, the floor is yours.

MR. MANGUM: Thank you, Your Honor. Let me just introduce Ben Jackson who will be presenting our tutorial. He's counsel of record. He also, as I indicated, was Senior Director of Legal Affairs at Myriad. He has a bachelor's degree in molecular genetics from UCLA.

As necessary to respond to any questions or to assist in the presentation, Dr. Roa will also participate. He has a Ph.D. in molecular biology from Northwestern University and is board certified in molecular genetics. So I'll turn the floor to Mr. Jackson. Thank you, Your Honor.

THE COURT: Thank you.

MR. JACKSON: Good afternoon, Your Honor.

THE COURT: Good afternoon.

MR. JACKSON: I'm grateful for this opportunity to talk about some exciting technology today.

The COURT: You know, I'm going to interrupt just before we begin. This is an obvious statement perhaps, and it's a legal statement, but I don't anticipate that we'll be getting into anything today that's confidential. We're talking about public patents and science, and I think there's been a great deal of discussion about all of this in the cases that preceded the filing of this suit, but I just want to make the attorneys aware that if we begin to venture into anything that any of you deem proprietary or confidential in some manner, notify me about that. We have an open proceeding

today and a few folks that are on hand to watch so let's just be cognizant of that. I'm sorry, Mr. Jackson. Go ahead.

MR. JACKSON: Thank you. So today we're going to talk about two main things, the basics of molecular biology and we're going to talk a little bit about molecular diagnostic testing. And this overview shows kind of the flow of my presentation, and I'll come back to this overview a couple times just to show us how we're moving through.

In the materials that we -- that we submitted to Your Honor there was an introductory video that were a couple minutes long. We can watch that again today but I'm hoping that you had the chance to watch that, and if -- it's pretty basic. If you'd like to watch it again, we can; if not --

THE COURT: I think I understand what we're talking about there. Go ahead.

MR. JACKSON: Okay. And this slide sort of recaptures what was in there anyway. The central (inaudible) --

(the court reporter asked counsel to repeat)

The central dogma of molecular biology states that DNA is used by cells to make RNA, which is then used by cells to make protein, and then proteins then do the work of the cell. And this is shown in this illustration right here. DNA is very simply illustrated here. These dots show that the DNA would, of course, extend far off onto each side. Genes will have

structures called exons and introns. We can talk a little bit more about those.

This DNA is used by the cell in a process called transcription to make a molecule called RNA. In that RNA the introns are removed by the cell and instead there are only exons left. Then in a process called translation the cell makes protein, and then the protein does all that work for the cell. It's this mRNA molecule that can be used in a laboratory by scientists to produce another thing called the cDNA. You'll probably hear that term.

Okay. So remembering back to that video, the video talks about how changes or mutations in a person's gene can lead to diseases or any other physical characteristic of that person. And so I will -- I would like to look at some of the other videos that are in this presentation. We'll start with this one illustrating the role of genetics in disease.

(viewing video)

I forgot to mention at the outset, but I hope this goes without saying, if any questions arise or anything, just feel free to interrupt me.

THE COURT: I won't be shy.

MR. JACKSON: Okay, good. So what we learn I think from these couple of videos and from these slides is that in biology form dictates function. The chemical composition of a gene dictates the chemical composition of a protein. A change

in the chemical composition of that gene can result in a change in the chemical composition or the structure of the protein, which then can affect its function, which can then lead to large scale changes in that person or that organism, disease, tall height, red hair, whatever it might be.

And so just going back to this example of the sickle cell, sickle cell disease. I like that example because it's so simple. A single nucleotide change, this chemical change from adenine at that one position along the gene to thymine, leads ultimately to this chemical change in the protein. Instead of glutamic acid, there's a valine. And that leads to a change in the -- the chemical properties of protein, they stick together, they clump, the cells change their shape and disease can result.

Cancer is often called the genetics disease in that genetic changes underlie the development of cancer. So the video mentioned BRCA1 and hereditary breast and ovarian cancer syndrome. That's a great example.

It also raises a good -- couple of terms that are good to understand, germline and somatic. So some genetic variations, some changes in genes, can happen in what's called the germline. That means that they're inherited down through generations. They can be passed on from parent to child. Those are called germline variations.

Other variations are not inherited. They occur during an

individual's lifetime in just some cell in their body, and those are called somatic variations. These are not inherited or passed along. And it's -- so most cancer arises randomly or sporadically, and it's caused by just these somatic changes.

But some families have more cancer than you would expect if it was just based on random chance, and these can be caused by germline mutations in important genes, such as the BRCA genes that can be passed on through families and you can -- researchers can see a pattern of cancer arising in that family.

So this kind of closes my discussion of the basics of what's going on inside the cell. And I'd like to move on to molecular diagnostics. So the idea in molecular diagnostics is to analyze important chemicals in a specimen taken from a patient, right, and to use those chemicals or analyze them in some way to figure out what's going on in that patient, if there's a disease, if there's a predisposition to disease, whatever it might be, whatever we're trying to discover about that patient. And many molecular diagnostic tests analyze DNA.

So let's take just a second to I guess differentiate molecular diagnostics from some of the more classical diagnostics that we might be familiar with.

THE COURT: I guess I do have one question that

comes to mind now, and that is we're talking about the current state of the art today; is that right? You're telling me about the state of science as it exists today?

MR. JACKSON: Yes.

THE COURT: Okay.

MR. JACKSON: And still today we do use some of these classical techniques. Microscopes for example could be used to diagnose sickle cell anemia. You could see the abnormally shaped cells under a microscope. But certain things can't be detected that way. For example, genes generally cannot be seen under a microscope. Certainly their -- their structure, their fine structure, what you might want to get out of that, can't be seen in a microscope. So scientists have devised laboratory processes to instead deduce that gene sequence because we can't observe it directly.

So what that means is we can deduce the structure of a gene that's floating around in the patient's body by quote sequencing DNA molecules in a test tube. And we'll talk more about how that happens, but that's -- that's the general idea of genetic testing, and it usually starts with a sample from the patient. We'll have thousands of cells and just kind of this gamish of -- of DNA coming out of those cells.

So what we're talking about here are laboratory techniques designed to do two things. One is called enriching a sample. So you want to enrich a sample for the DNA of

interest because it's kind of lost in that whole milieu of DNA that came out of the patient's cells so you want to get more of what you're looking for. And then once you've got that, you can determine the structure of that molecule, and then from that work backwards to deduce what was originally floating around in the patient.

So the first step in this process that I talked about is enrichment. And let's talk a little bit more about that. So as I mentioned, the DNA extracted from the patient's cell is random, whole, genomic DNA. It's just this mixture of DNA molecules, of chromosomes and all that. So the three billion nucleotides of the genome can interfere with an efficient analysis of one particular portion that you might want to study, such as, you know, the 5,000 to 10,000 nucleotides that are in a particular gene that you're interested in.

So what you can do, even if you were to isolate, you know, extract away those genes from that initial mixture, there's still not much material there, and the laboratory processes that are used today are not sensitive enough to really sequence that very well, so that they need more, they need more material to work with. And this is called enrichment and target amplification.

So typically this is done by a process called PCR, which stands for polymerase chain reaction. This is a chemical reaction that is used to synthesize numerous DNA molecules

with a specific uniform sequence. And we'll watch a video that's going to show how that happens.

(viewing video)

So that's a little bit -- a little bit complicated, but the basic idea is that the -- the polymerase -- the reagents, the primers, the polymerase and all these things are used to generate a lot more DNA molecules having the sequence -- the structure of interest so that those molecules can then be used for sequencing, or whatever else you might want to do. In this case we're mainly talking about gene sequencing, so that's what you would do with the resulting molecules. And this was mentioned in the video, the fact that the newly synthesized DNA vastly outnumbers the original DNA. Again, that's by design. That's for a purpose there. And, again, it's these new DNA molecules that form the starting material for a sequencing reaction.

Let's talk a little bit about how PCR --

THE COURT: Are there conventions on how long or what portion of the DNA strand is replicated during that process or does it just vary?

MR. JACKSON: It's -- it can be really any portion that you want, but there are some -- there are some conventions when you're designing your reaction; right? And we talk a little bit about that later when we talk about a primer design, but you want to avoid certain portions of --

certain sequences of DNA that might be problematic because they might be nonspecific for what you're looking for or they might hit a region that varies between individuals. So there -- there is some general principles that -- that scientists use in -- in designing these reactions. But it really depends on whatever the scientist wants to know; right? If the scientist wants to know what the sequence is at a particular point, they can design primers to -- to synthesize DNA at that region and then they can analyze it.

So we talk about designing a PCR reaction, which may be a little bit of an unfamiliar term. What we're talking about there is designing what reagents, what chemical reagents are going to go into that reaction and what that reaction will accomplish ultimately. Again, what is your goal here? What do you want to know? What DNA molecules do you want to come out of here? And what kind of the key component in there is the primer, the design of the primer, because that will define what the ultimate molecule synthesized in that reaction will look like, yeah.

So an important point here is that the DNA molecules that are synthesized in a PCR reaction are different from -- have a different sequence from the DNA that came out of the patient's cell. And it's --

THE COURT: Say that one more time.

MR. JACKSON: The DNA molecules that are synthesized

by PCR are different from and have a different sequence from the DNA that came out of the patient's cell, the DNA molecules that came out of the patient's cell.

THE COURT: Why?

MR. JACKSON: I'll show you. So you see this -- this blue molecule is meant to be the -- the patient's DNA. This is what came out of the patient's cell. And let's assume for this example that it's been fragmented, just chopped up randomly; right? It will be, let's say for this example, about 1,000 nucleotides long, 1,000 of those bases attached together.

Now, the primers are these little red arrows. Now, this is all very simplified but, of course, it's a molecule. It's a chemical. But this is just to show the principle. These primers are quite a bit smaller. They're 15, 20, 30 nucleotides long. They will hybridize to that patient's DNA. As we saw in the video, these DNA molecules will be produced.

Now, look at these molecules. They are smaller than this bigger one. They are, as it says here on the slide, complementary to a region of this original DNA. But they're a different molecule, and they have a different sequence in that this overall sequence of the patient DNA looked at as a whole is different from this sequence of this PCR synthesized DNA as a whole. Any two DNA molecules -- basically think of it this way. Any two DNA molecules that are different lengths by

definition can't have 100 percent the same sequence. And also the sequences at the ends of these will be different; right? Let's say the end of this molecule has this particular structure. Well, the end of this molecule is going to be different.

THE COURT: Of course, the portion that's pulled out of the original patient DNA, and it's reflected there, that's exactly identical in every instance?

MR. JACKSON: Sorry. So you're saying --

THE COURT: The strand, to use your depiction here, does the portion between the primers that is, I'm going to say, excised or cut out of the patient DNA strand, that's the portion you're trying to replicate, and for this process to work, the replication ensures that you have an identical replication every time, is that true?

MR. JACKSON: Yes, kind of. So remember that -- that this -- this blue streak is the molecule that was excised out of the patient. So these molecules are not excised out. These are synthesized, using this one as a starting material and as part of the process. This blue molecule right here is what came out of the patient's cell.

THE COURT: Is synthesized a fancy word for copy?

MR. JACKSON: I would say no, in that synthesize is broader; right? Synthesize means to connect chemical pieces together to form a larger chemical; right? And so that's kind

of a general idea of synthesize. Does that --

THE COURT: Let me just think about that for a minute.

MR. JACKSON: So think of maybe connecting links in a chain together. That would be maybe analogous to synthesizing a chain.

THE COURT: I understand. Okay.

MR. JACKSON: Now, copy, that's a term that is very often used in the science to say, okay, we're going to copy this DNA. Copy, of course, suggests an exact copy, right, which is not what's happening here, at least insofar as an exact copy of this entire molecule. Instead what's happening is a portion of that molecule is being synthesized.

THE COURT: Well, let me use your metaphor. And I'm not trying to argue with you. I just want to make sure I understand as precisely as I'm capable today your presentation. But let's use your analogy of a chain, and let's assume links of different colors, and it's a 10 foot chain, and you want to replicate one foot from the center of that chain. Your synthesized chains will be identical to that foot that it existed in the 10 foot strand every time; is that true?

That is, each -- if we went and looked at any single foot that's synthesized later, we assemble it with the different color of the chain links, and compare it with the original

strand, the original chain, that foot that we were trying to copy or synthesize will look exactly the same as each of the other chains that we try to withdraw from; is that right?

MR. JACKSON: In terms of its sequence of nucleotides over that stretch, in some applications yes and in some applications no, because in some applications this molecule that is being synthesized you'll use maybe modified nucleotides, you'll add a label or something else. In fact often these primers have a chemical label attached to them, which would then make them different. So, yes, so that's the answer. In some applications, yes, the sequence of those -- of this portion of this molecule will be the same as this, but in other applications, no.

THE COURT: By design?

MR. JACKSON: By design, yes.

THE COURT: Is there a different word for that if you are synthesizing or replicating a portion of the strand that you want it to be different after you go through that process, is that still called -- is it still synthesized, PCR synthesized, or is it something different?

MR. JACKSON: I think you would still call it a PCR synthesis.

THE COURT: Okay. All right, thank you.

MR. JACKSON: So now let's move on to a little bit more discussion of primers, unless you want to -- anymore

questions on the PCR generally.

THE COURT: Some may come up, but I'm tracking with you so far. Thank you.

MR. JACKSON: So we've talked a little bit about primers and their role in PCR, but let's talk a little bit more in detail. We've talked about the general principles of PCR; right? You use an enzyme. You have primers. You heat. You cool. These are, again, the general principles, but these principles don't allow one to necessarily design a specific PCR reaction for a specific molecule that you want to generate. For that the most important part is the design of the primer because the primers will dictate what that synthesized molecule will ultimately look like. And for that you need some knowledge of the sequence, the structure, what are you looking for.

The COURT: That's because the primers define the start point and the end point; is that right?

MR. JACKSON: Yes, exactly. And so primers are unique to each reaction. And like we said, the sequence of the primers determine what the chemical composition of that ultimate DNA will be. And this might help to illustrate a little bit of what we're talking about.

Let's imagine -- this might be a little bit hard to parse out, but this is actually two DNA -- two very short DNA strands, one right here that I'm calling a primer, one right

here that I'm calling a target DNA. So what the scientist does is he looks at this target DNA and he says, okay, well, here is an (A), an adenine, a cytosine, a thymine and a guanine.

So if I wanted a primer that could -- that had the chemical properties to attach to that -- to this target DNA, what would I want it to look like? Well, he'll use his knowledge of this sequence and his knowledge of these principles to design a primer that will have this sequence, and it will have these exact chemical properties such that they combine. So oxygen is attracted to this nitrogen. That's just how it works chemically; right? And that's how these things are designed.

So let's move on to a --

THE COURT: So to select -- well, I'm jumping ahead of you maybe. To select the primers that attach at the right places in the DNA strand, the scientist is examining the nucleotide sequence and looking for a sequence that is long enough to be unique so that it -- the scientist can design a primer that will attach only at that place, and the structure of the DNA sequence -- or the nucleotide sequence will determine how long the primer has to be; is that right?

MR. JACKSON: Yeah, yeah. Sounds like we might not need to watch the next video because you got it.

THE COURT: Let's watch it.

MR. JACKSON: But you're right. That's exactly what we're talking about.

(viewing video)

So just like Your Honor said, the length of the primer and its location, all of these things have to be taken into account if you want to design an efficient PCR reaction. So let's just take just one quick step back.

THE COURT: Why is that important, efficiency? You said to design an efficient PCR reaction.

MR. JACKSON: Well, let's see. So here we're saying that this primer has four nucleotides; right? Typically they'd be 30, but let's just say it's four. Now, let's say this one is supposed to have a thymine right here. Let's suppose instead it had an adenine. It would not bind this target DNA very well. And if that adenine was -- if that wrong nucleotide is at the very end of a 40 base pair of nucleotide primer, it might still bind but not well; right? So you might get some results but not great results, especially if this is at a position that varies amongst people; right? All people have different DNA, and it's different at just random positions all over the place.

And so if this happens to be a position where a certain population has an A, another population has a T, you don't want your primer to sit there, because it will work great for the people with the A but it won't work great for the people

with the T. You've Lost your efficiency, especially in a large scale laboratory operation.

So this really just sort of reiterates -- this slide reiterates what we've already seen and discussed. Except for one last point. This is one about optimization, and we've -- we've kind of hinted at this. And that is that often, especially again in a large laboratory operation, there's some optimization that needs to take place. You try the primer. You design it. You think it's going to work great. You put it into the test tube. You put it into the thermocycler and you don't get great results or it amplifies a bunch of things that you didn't mean to do, whatever the problem might be. So you go back and you try to figure out what was the problem, what was the error in this design and you redo it. And that happens often.

So now just sort of to keep within context and help us know where we're going. So all that we've talked about here is just generating enough DNA to do your analysis.

THE COURT: Did we talk about how long that process takes, that enrichment process?

MR. JACKSON: No, we didn't really talk too much. So like a PCR reaction can take a couple hours, let's say, because what you'll -- what you'll do is you put your test tube into this machine, the thermocycler, and it cycles the temperature up and down, up and down to 90 degrees centigrade

to down, and that just -- and it will do say 30 cycles of this fluctuation in temperature to repeat this chain reaction. And we talk about hours, on the order of hours.

So once we've done this enrichment, now we've got enough material to work with, we can do the sequencing. That's what we'll talk about here. And again recall -- again, to keep context and keep track of where we're going, the ultimate goal here is to learn what is the patient's gene sequence? What's the structure of the gene in the patient's body and what might be the implications for that structure as far as a disease or something like that?

So once we've got enough of these molecules in a test tube, we can then do what's called sequencing. I put quotes in that because let's talk a little bit about what does that even mean to sequence a molecule; right?

Okay. So sequencing is the process of deducing what the structure of an original molecule was from these other synthesized molecules. And I say deduce. Again, I put that in quotes and I use that quite a bit in this presentation, but there's a reason for that, is that as we discussed before, we don't directly observe the original DNA that came out of the patient's cell in these processes that we're talking about. We can't.

Instead, we generate a bunch, numerous, billions of DNA molecules and analyze those in a chemical reaction and from

those deduce what was originally there. And there are two primary types of sequencing by which we do this. Let's talk first about Sanger sequencing.

Sanger sequences -- sequencing is often called dideoxy sequencing, and the reason for that is there's a special chemical reagent used in that reaction that's called a dideoxynucleotide. And we'll talk more about why that is or why that's important. It's in this video, and I can explain more if you'd like to hear a little bit more but, again, Sanger sequencing is generally synonymous with dideoxy sequencing. So let's watch this video that shows it.

(viewing video)

I just want to pause the video right here. I think this is a good place to stop just for a second to explain what dideoxy is because it's kind of -- it sounds like a very technical word but it's quite simple. What it really means is it's a nucleotide that can't be added to; right? All of the standard nucleotides they have these chemical pieces that are just waiting to accept the next nucleotide, its corresponding piece on the next nucleotide. A chemical reaction can take place to join them.

But these dideoxynucleotides are designed to not -- they don't have that receptor spot. They can't be added to. So that terminates the chain. And anytime one of these things gets added, terminates the chain.

THE COURT: Are they A's, C's, G's, T's or something different?

MR. JACKSON: No, they are.

The COURT: They're just modified in a way so that they can't receive -- if it's an A it won't attach to a T for example?

MR. JACKSON: Yeah, it won't attach to anything. Here, let me run real quick. So right here, you see this -- so we talk a lot about these A's, T's, C's and G's; right? These are kind of the working end of DNA, but there's also this backbone part. And right here the structure of this part here determines whether you can add another thing on; right? So here, what if -- if this molecule is missing this P-O-O-O, missing that entire oxygen part, then it can't be added onto. It's chemically inert for these purposes. It's dead; right? You can't add anything more on. So this chain ends right here if that happens.

So if this was a dideoxycytosine instead of a regular cytosine, it would stop right there.

(viewing video)

And, again, this slide really summarizes what we just saw in this video. A lot of the text on these slides are there for -- for your later reference. We won't read everything here today. But primers are used in this -- in this sequencing reaction in very much the same way that

they're used in PCR. They need to be designed to anneal to a certain spot and to prime that chemical reaction.

And, again, this just sort of shows again how you look at -- or how you detect the molecules as they come off of that gel and you can then determine what the -- what the nucleotide was at each position. So that's Sanger sequencing. That's one way to do sequencing.

Another way that we're going to talk about today is next-generation sequencing, which is a term that is typically applied to any sequencing technique really after Sanger. And there are a lot of different next-generation systems with a lot of different chemistry going on, but one common defining feature is what we call multiplexing.

What this means is that instead of a single reaction in a single test tube, instead using next-generation sequencing you can have hundreds of thousands of sequencing reactions taking place all out once in one reaction.

THE COURT: When did scientists start using next-generation sequencing?

MR. JACKSON: That's a good question. I'd say one of the earliest -- I might turn to Ben Roa to help me out here.

Dr. Roa.

DR. ROA: In the research field it's been probably in the past five to ten years. More recently it's been used

in the clinical laboratory setting.

THE COURT: Thank you.

MR. JACKSON: Thank you, Ben. Okay. So beyond the enrichment that we already talked about, the PCR synthesis, next-generation involves two additional chemical synthesis reactions. Typically there's another amplification reaction, but then also there's what we would call the real sequencing reaction.

And what happens there is -- well, actually, if I can take a minute over here at the board. What happens is -- I don't know if I should use dry erase on the paper. So you've got your -- so other counsel can see. You've got your other -- your single strand of DNA molecule that came out of your PCR enrichment step. And it's say tethered to some surface; right?

What will happen is -- there's a little primer here. You'll hear a lot of these things repeated, a lot of these concepts and reagents repeat. And so polymerase will be used again and new molecules will be added. Let's change the color just to make it a little bit easier to see. New nucleotides will be added as you go corresponding to what is on this molecule; right? Maybe here is an adenine, here is a thymine, here is another adenine, guanine. And at each step, as each one of these things is added, the machine, a little florescent label will be released and will be excited by a laser. The

machine will detect that excitation, that light that comes off, and say -- and so to each adenine there might be a green label, to each thymine there might be a blue, guanine, red, cytocene, purple, I don't know, whatever else. And then as each one is added, a little flash of light goes off. And so then the machine can detect that an adenine was added.

So as this thing is synthesized in this reaction, at each step the machine is reading each one of these steps and is saying, okay, an adenine was added there, a thymine was added there. And so that's how that works. It's called -- it's often called sequencing by synthesis. That's kind of a common term.

And that's -- that is in a nutshell next-generation sequencing. And the reason that this allows for multiplexing is that when you're over here on this microchip let's say, you can have just millions of these set up, and you can do them all at once, and it allows for this multiplexing that we talked about to make it more efficient.

So the result of all of this -- so, okay, let's go back to our overview and kind of touch base again, where are we. We've enriched for the molecules that we were interested in. We've made those. We've now run them through a sequencing process, through a sequencing chemical reaction, and the output of that reaction is a sequence, chemical structure, a depiction of a chemical structure in the form of a sequence, a

nucleotide sequence.

THE COURT: Let me ask you to stop for just one moment.

(Brief Pause)

Thank you. Go ahead.

MR. JACKSON: So the output of this chemical reaction is this machine is -- is detecting these flashes of light that's computationally analyzed, and the machine is reading out or reporting out, outputting, this sequence that corresponds to the structure of whatever that molecule was. And so you get these, what you've often seen, these strings of letters. These are called -- we talk about these as sequences. Now, they correspond to molecules, but these are the sequences; right? These are the letters; right?

Well, now you need to kind of figure out what all that means; right? That doesn't really help you. That doesn't help the patient sitting in the doctor's office who wants to know whether she's at increased risk for breast cancer; right?

So the next step is we move on to some computer analysis. These molecules that are going to be analyzed and sequenced in the sequencing reaction are typically very short molecules, 100 nucleotides, 200, something like that, whereas the gene could be thousands.

So what needs to be done is researchers use a computer to analyze the raw short sequence data and to quote stitch them

together informatically to deduce a composite sequence that represents all of those molecules together. And in the abstract that's kind of hard to -- that's kind of hard to think about, but I think the video illustrates it fairly well.

(viewing video)

And this process is again summarized here on this slide. I kind of like this picture because it shows more or less what's happening; right? We don't know what the patient's sequence was. Through the enrichment and sequencing chemical reactions we -- we get a bunch of these very small sequences. But then computer software is used to align up these raw sequencing -- these raw sequences, assemble them to where now they're starting -- we see where they overlap. Where do they overlap? And as we start to read all of that off, we end up with a composite deduced patient sequence, and then from that we can start to make clinical decisions or try to figure out what's going on with this patient.

So the next step, kind of the final step in that -- in that computer analysis is now we know what the patient's gene sequence was. We've now deduced what is floating around in that person's arm from this process, this long process. We now have deduced what's in there. Well, what does that mean? Clinically what does that mean? It doesn't help for me to know that that's an adenine here rather than a thymine, or that there's an adenine here. Let's figure out what does that

mean.

So what we will do -- well, let's watch the video that shows how this is done.

(viewing video)

This might help to illustrate what we're talking about here, is researchers will use a computer, computer software and this data that they got out of the sequencing reaction to try to align these sequences and see what the differences might be. Here this shows some reference or wild-type sequences that can be used against maybe a patient sequencing. You can see that right at this position, whereas these two reference sequences have an A, an adenine, this one has a guanine. That's a difference.

Now, we don't -- we may not know what that means clinically, but at least we know this patient has a difference here. Here is another one. Whereas this reference wild-type sequence has an AG right here, an adenine guanine, in the patient those two are missing, and that might have clinical significance. We figure it out.

And so if there is a variation, scientists can then go on to try to classify that variation. Does the variation change the protein in such a way that it doesn't work anymore?

THE COURT: Where is the wild -- where do the wild-types come from? Are these from public databases?

MR. JACKSON: They can come from public databases,

yeah.

THE COURT: And do you often compare your patient DNA strand against multiple wild-types or is that silly? Is there one that's a standard or do you use -- do multiple overlays? How does that work?

MR. JACKSON: It can depend on what type of -- if you're doing research to try to figure out how much variation there are across populations, you might want to compare multiple reference sequences.

I think that typically -- and Dr. Roa can help me out here, but I think that typically in clinical sequencing, if you're trying to figure out stuff for patients, whether they should be treated or not, you'll typically use just one standard reference.

DR. ROA: Yes.

THE COURT: Are there uniform wild-types that are generally accepted among scientists to be the model that you use for a specific gene sequence you're trying to compare against?

MR. JACKSON: Again, I'll defer.

DR. ROA: Usually there is a consensus wild-type that is annotated in the databases and in publications.

THE COURT: Is that true for our BRCA1 and BRCA2?

DR. ROA: Yes, there is a consensus wild-type.

THE COURT: Okay. And it's a single wild-type, a

single -- is strand the right word? There's a single sequence?

DR. ROA: Yes, there is a single sequence that is entered as a reference. However, as Ben Jackson pointed out, there can be variations from that sequence that are benign or normal.

THE COURT: Right.

MR. JACKSON: And so the researchers can use this single reference sequence, and if they see again a difference, if they see a difference, they'll try to decide, okay, there's a difference from the reference but that doesn't mean that it's harmful. It could just be a variation, a benign variation, or could be something that radically changes the protein and we need to do something about that.

And so this can be used to diagnose disease, predisposition to disease, like responding to a particular drug, any kind of the things that we now tend to call personalized medicine. These -- these are the diagnoses that can come out of this whole process.

So that -- that's pretty much mostly what we're talking about here. What I've added here at the end is a little discussion about large rearrangements. But for the most part this is the process of molecular diagnostic testing for Genetic testing.

THE COURT: Gosh, it sounds really easy.

MR. JACKSON: I'm sure. Again, if there's anything you want me to go back, we can talk about it.

THE COURT: No, but this is helpful I think to address, so let's talk about this.

MR. JACKSON: Okay. So now all that we've talked about so far is typically we've been talking about single changes; right? We talked about the sickle cell example. I love the sickle cell example because it's so simple. There's just one chain and one nucleotide in the gene and that causes disease, or here, two nucleotides, same thing. But that's not all that can happen. That's not all that can go wrong. A lot of other things.

So what can happen is what's called a large rearrangement, which is a chain of hundreds of thousands of nucleotides within this gene can be removed, and this can just be an error. As the cells are replicating, something happens, something was missed. It's just not perfect. It's nature. It's not perfect. And so these large rearrangements can take place.

And these traditional sequencing techniques either cannot detect those changes, such as in Sanger, or cannot be very good at it, such as next-generation sequencing. So you got -- so scientists have devised other ways to detect these large rearrangements.

Two laboratory techniques used today are MLPA and

microarray. Now, MLPA stands for multiplex ligation-dependent probe amplification, which is a mouthful.

THE COURT: Pause for one moment.

(brief pause)

All right, thank you.

MR. JACKSON: Sure. So that's a mouthful. We'll just call it MLPA, much better. So this involves binding of a DNA probe to a DNA sample and then detecting that binding or hybridization event in some way. And much like PCR primers, MLPA probes are relatively small, on the order of 70 or so nucleotides long, and they are also synthetically created and designed to bind to a particular -- hybridize to a particular region or a particular molecule having a particular sequence.

Now, this illustration is possibly more detailed than we need, but we'll try to run through it quickly.

THE COURT: How do we know -- when do we get to this step commercially? If you're in the lab, do you start with the Sanger sequencing and next-generation and you run it, and if it -- you get results that seem unusual or not what you expect, then you move on to a different kind of sequencing?

MR. JACKSON: You could. You could do it sequentially. You could do it in parallel.

THE COURT: I guess a better question, maybe the one that I'm really wondering, is when do you employ any of these different techniques if you're a researcher?

MR. JACKSON: So most -- well, from what -- again, Dr. Roa can help me out if I'm going far afield. But most mutations in say the BRCA1 gene, because that's one that I'm fairly familiar with, are on that small order. They can be detected by just the sequencing reactions that we talked about, Sanger, next-generation. They're small. So most of them can be detected that way.

So one potential approach to doing clinical testing is to do that first because that will catch most patients who might have a mutation. But then if the patient has a particularly troubling family history where you say, boy, I really think something is going on here, but nothing came out of the sequencing, let's do what they might call reflexing. So you reflex to this large rearrangement testing to say there is a good chance this may -- this may catch something that wasn't in the first screen.

So I don't know if that's helpful, but that's -- that's a -- a testing strategy that can be employed.

THE COURT: And the choice to use, if you know, or if there is -- why does a researcher choose to use Sanger or next-generation sequencing? Do each present some advantage and disadvantage?

MR. JACKSON: Yes.

THE COURT: And so it depends on what you're trying to achieve?

MR. JACKSON: Yes, exactly.

THE COURT: All right.

MR. JACKSON: Yes. And they'll often be used in conjunction with each other, especially now as next-generation is relatively new, relatively. Sometimes it's not terribly efficient at finding mutations in certain regions of genes and that type of stuff so you might supplement with Sanger, which is battle tested and proven to supplement for those regions. That's -- that's commonly used.

So MLPA, again, to try to fund these big changes, basically what happens is you've got your target DNA. You've got these probes here. You put them all in solution together under certain reaction conditions, and if this target region is present, the probes will bind. If it's not present, they won't bind. And you can then detect was there a binding or was there not? If there was no binding, or if there's less binding than you expected, you can deduce from that that that region was missing.

And that's kind of maybe better illustrated here where you can see that this is kind of a way to think of maybe a gene that has four exons here, four regions of interest here, one, two, three, four. You do your probe binding and PCR synthesis. You get a bunch of these PCR molecules. Then you measure the amount of those molecules. And if you get this expected amount, you can deduce, hey, that patient had all

four of those regions that I was expecting.

But here, let's say this patient has a mutation, a large rearrangement, where this whole section, which can be thousands of nucleotides long, is missing from her DNA. So then you do that same process, but when you go to measure the PCR, you notice this is missing here. And so then you can deduce that that -- that that big, large mutation has taken place.

THE COURT: Does that just tell you that in that segment that's missing there were one or more nucleotides that were not in the order you expected? Does it tell you anything more than that?

MR. JACKSON: It just tells you that they're missing; right?

THE COURT: That the segment is missing?

MR. JACKSON: Yes.

THE COURT: From your result?

MR. JACKSON: Yes. But you can deduce from that that they were also missing in the original, in the patient's DNA as well.

The COURT: But you don't know what or how many nucleotides were not in the order you expected or --

MR. JACKSON: Sometimes you don't know that fine detail. Particularly with MLPA you might not know the exact detail of where did this thing get chopped off exactly, or

what was the order -- they get flipped around in order. You're right. You won't be able to tell in that fine level of detail, especially with MLPA.

THE COURT: Are there probes that are -- I mean is this like a wild-type sequence? Are there probes that are consensus everyone agrees this is a standard probe nucleotide sequence that will run against this strand, looking for these segments, or is that -- is that a commercial thing that researchers view differently?

MR. JACKSON: It's more the latter. I mean you can design the probe however you want, to have whatever properties you want. As a practical matter there's really just one main company that provides say MLPA kits to most organizations, so in this case there actually is probably a standard probe for each region that you're trying to go for, but that's more just a consequence of who provides it. But if you wanted to design it differently, you could.

THE COURT: Is there just one probe that you typically run against a strand DNA when you're looking for a specific -- well, here you've got four segments, or would you --

MR. JACKSON: So these will be different probes for each one of those regions. And that's why they call it -- the M in MLPA is multiplex, and that's again a term that comes around every once in a while. All it just means is you do

multiple things at once. So you're doing multiple probe hybridization reactions at once. So you want to see, hey, is this -- is region number one there? We'll use the probe for region one. Is region two there? We'll use the probe for region two.

THE COURT: All right.

MR. JACKSON: So the last thing we'll talk about is another way of doing large rearrangements. Remember, there were two ways of doing sequencing, Sanger and next-generation. There are two primary ways of doing -- of determining whether there's a large rearrangement, MLPA and now microarray.

The principles of microarray are fairly similar to MLPA. It uses probes, synthetic probes, that are designed to hit a certain region, to hybridize to a certain region, just like we were just talking about.

The difference being that -- well, here is a little illustration to show this process. You can take the patient and the reference DNA, put them into a vial, pour them onto this microchip. Now, if we were to be able to zoom into this microchip, we'd see that each of these little squiggly purple lines is actually a DNA molecule. It's a probe molecule that is designed to hybridize to a certain region of the DNA, just like this; right? It's designed to hybridize here, or here, or here, or wherever it might be.

And so these little probes can be tiled all the way

across the length of the gene. You throw your DNA onto that microchip. You let it sit there under certain conditions that will allow it to hybridize if it's there or not hybridize if it's not. A machine reads the fluorescence of those DNA molecules. They've been chemically modified to light up when a laser hits them.

The machine reads that and can tell the relative proportion of patient versus reference and can tell whether -- whether this region is missing or not, or maybe duplicated. Maybe there's -- maybe this region appears twice in this person's gene when it really should only appear once. So you'll get twice as much green as you expected. Or if it's missing, you'll get either zero green or half as much green as you expected. That's how you're able to detect on that hybridization or not hybridization. And that's --

THE COURT: Will you go back two slides -- one more. Do you recall if there's a -- oh, there are, okay.

(Brief Pause)

All right. That's very helpful. Why don't we do this. Oh, go ahead.

MR. JACKSON: Can I just make just a couple of closing --

THE COURT: Oh, please.

MR. JACKSON: -- remarks. I was thinking back to your question about are there standard probes for MLPA, is

there kind of a standard sequence that you would use. I think one way that might be helpful in thinking about probes is we had kind of a lengthy discussion about primers and how they are designed, and that for each reaction they are designed to give whatever properties you want for that reaction, and that you use the -- the knowledge of -- of a sequence of the molecule that you're trying to synthesize to design that primer. And all of those principles essentially apply to designing a probe; right? You will -- you'll get the sequence that you want to detect, to hybridize to. You'll design your probe in a certain way that might involve some optimization for the same reasons that we talked about primers need to be optimized, the right length, the right portion, does it hit a variable region, all of those same principles apply to probe design. Yeah.

THE COURT: The techniques that you've talked about in your presentation, these are standard techniques. They apply both in the context, for example, of BRCA1 and 2 testing but also for example sickle cell testing? These are uniform principles of genetic, what we would say, sequencing and testing?

MR. JACKSON: At the highest level of generality that's true. But once you get down to the details of the reaction that's going to take place, they'll not be true. Like let's say a primer that will work well for doing a PCR

reaction with BRCA1, a portion of BRCA1, would not work for sickle cell.

THE COURT: Right. And maybe these two are good examples to contrast with each other. I gather, given that the sickle cell question turns on such a discrete issue, it's easier to isolate, the probes and primers are shorter and the like, but the processes are the same?

MR. JACKSON: Yeah. I mean the general principles that apply -- again, the general principles of PCR will apply generally, PCR, sequencing, same thing. And so then, you know, just to summarize, we look at the basics of biology. What -- why do we do molecular diagnostics? Well, you know, we've got to get more material. That's why we do enrichment. We can do then sequence that material, analyze those results to get a clinical output, yes or no is there a problem. And then we talked a little bit about large rearrangements. Thank you, Your Honor.

The COURT: Thank you.

Mr. Gaede, why don't we take a moment. I gather you'll have a significant presentation from your side as well. We'll let our court reporter stretch his fingers. We can swap out whatever gear you need to swap out. You do have something more? You don't just adopt that presentation wholesale, do you?

MR. GAEDE: I wouldn't want to copy it, no.

THE COURT: I understand. All right. Let's take a brief recess, about 10 minutes, thank you.

(recess from 2:41 PM until 2:56 PM)

THE COURT: We didn't cover this at the outset but everybody will have a chance to fully respond to everything they've seen from the other side too, so you're all aware of that, Mr. Mangum.

All right. Mr. Gaede, hello.

MR. GAEDE: Hello, Your Honor. First of all, does the Court need any extra copies of his presentation? We have those here if you'd like them.

THE COURT: I have them here. I'm pretty much just focused on this so I don't lose the --

MR. GAEDE: Okay.

THE COURT: -- speaker, but thank you.

MR. GAEDE: Absolutely. All right. So let's start out. I think a little bit of basics would help here and start from the beginning, which is DNA. And what is DNA? And what are the rules by which DNA operates, the natural rules by which it operates?

So obviously DNA is found in human cells. It is found in humans in our chromosomes. As a matter of fact, our chromosomes, we have two copies for each chromosome, one comes from the mother, one comes from the father. They're not exact duplicates. They actually vary. And it also depends on then

why we start to vary, why we have brown eyes, why we have blue eyes, why we have some hair, no hair, all those types of traits.

And the genes are on both chromosomes. So BRCA1 is on both chromosomes, 17, and the duplicate. And that's important to remember, and there can be differences between the chromosomes because they come from the mother, they come from the father, but it's DNA. And that's what the chromosome -- and it's one long strand of DNA.

And in fact really they think of the whole human genome as one continuous strand from chromosome 1 all the way to the end of chromosome 23, that is then broken up into the chunks of chromosomes, but it's all -- the genome is that entire sequence that runs from number 1 to approximately three billion, give or take, you name it, however many.

So you've got your basics. It's in the chromosomes. You have then, of course, the familiar double helix structure. We'll talk about that a little bit. But DNA is DNA, deoxyribonucleic acid, and it's in humans, it's in amoebas, it's in plants, and it can be made by man. The same molecule can be made by man and by nature.

So the question of that molecule made by either nature or by man in your body, Mr. Mangum's body, or in a test tube, it's still deoxyribonucleic acid. Now, what is deoxyribonucleic acid? The structure of it is the same. So

let's start with the structure, because I think it's important to understand what the structure here is.

You have your single DNA nucleotide, and you have your backbone. So you heard Mr. Jackson talk about the backbone, the nucleotides. Well, let's focus on those a little bit more because I think that's an important concept to make sure that we have.

Yes, there's the language of DNA. It's like the alphabet. We have 26 letters in our alphabet. There's four in the language of DNA, T, A, C and G. And like our alphabet, innumerable words can come out of C, T, A and G. So we have the four different bases, that's all you're ever going to see, in a strand of DNA, A, T, C and G. And you see how we've depicted -- the chemical structure is the same whether it's made in a test tube, whether it's made in your body, same structure, A, T, C and G.

Then how do those two strands come together? They come together through a natural law called Watson-Crick base paring. So James Watson, Francis Crick, famous in the 1950's for discovering the famous double helix structure of DNA. People knew there was DNA in the body. They just didn't know exactly how it existed. They knew there were chromosomes in the body. All that was known.

Watson and Crick and their natural law of base pairing figured out the notion that it's two strands of DNA that

hybridize -- you're going to keep hearing that word -- hybridize across these nucleotides following this natural law, A can only bind with T, C can only bind with G. C cannot bind with T. G cannot bind with A. And that natural principle governs everything you just heard Mr. Jackson talk about, everything. And we'll talk about why that is.

So now we have the second strand. Obviously the A has to match that T. The next nucleotide -- and, by the way, if you don't mind, sometimes I like to go point at the screen. Is that okay?

THE COURT: Make use of whatever space you need.

MR. GAEDE: It helps me a little bit. Each one of these is a nucleotide, across it's called a base pair. They're bases. They have pairing. So A and T are pairing there. That's a base pair. Obviously G, it's going to fit in with C then. And C has to fit in with G there in order for those to hybridize.

And there's what's called a -- it's a fancy word, noncovalent interaction between the two that holds them together called a hydrogen bond. Think of it like two magnets that stick together. They're technically not fused together, but they are joined together by the hydrogen bonds. So two magnets coming together is a useful analogy as a way to think of it -- not the same, I grant you, because one is magnetic force, one is a hydrogen bond, but it's similar in concept.

Okay. Now, how does DNA replicate? Because everything you just heard takes advantage of the properties of DNA to replicate. It occurs naturally. How does this happen? Strands separate, and each strand, because of the law of Watson-Crick natural base pairing, provides a perfect template for the other strand in order to replicate, because right there at the end, a T must come in, and lo and behold that's what it is. And it must follow this law.

So each strand contains information to replicate the double strand and to replicate itself. That's important. Why? Because in our bodies, as we're sitting right now in this room, our cells are constantly dividing. It's going on in your body. It's going on in my body. And that means that DNA has got to replicate because it has to then go into the daughter cells, the replicated cells. All right. So that process of separation in a replication is going on all the time in the body.

So what happens? There's the famous DNA double helix, begins to separate. This just makes the point I made before. It will come in then using what you call -- you heard this term polymerase. It's a form of a protein that exists. It helps -- DNA polymerase helps all this process happen. It's what happens naturally. So you heard them say Taq Polymerase. That's one that actually occurs in nature. And we have a polymerase in our body. All this helps this replication

process happen.

And then you're going to see them come in, so that each strand contains the information to make an exact duplicate of itself. So each strand is very important because each has the function and the ability and it does make a duplicate of itself. And so cells need that ability in order for there to be proper replication of the cells, a process which goes on in our body all the time. So a single strand of DNA contains all the information necessary to specify the sequence of the double-stranded DNA. Okay.

So you'll have this process. And you're going to see this, Your Honor, and I don't know the exact reason why. I'm sure Dr. Pribnow, who actually has a sequence of DNA named after him called the Pribnow Box from 1975 based on his early work in this area, could probably tell you, but you'll see this convention of five prime and three prime, and you probably -- you may have seen that in the things you're looking at. It talks about the direction of the DNA.

So when you think about the DNA replicating and coming apart here, what's going to happen is it's going to replicate in two directions. One is going to be this way, one is going to be that way. And based upon the strands, you're going to have replication going in both directions. Okay.

So here you have it, continuous synthesis. You might have a discontinuous synthesis. And what that simply means --

again, a little bit complicated, but actually I think it's an important concept. This is continuing to unwind, and so these strands are becoming separated, okay. And you have to somehow prime it to start it, the sequence of making the double strand that's being filled in. So this way it's just following the strand as it unwinds. This way though, as more is unwound because it's going this way, you have to keep priming it. And there are natural primers that do that.

I want to make sure. Dr. Pribnow, did I get that right?

DR. PRIBNOW: Yeah, sure.

MR. GAEDE: Okay. I want to make sure. So then just to kind of -- when you think about it in our chromosomes, this long sequence of DNA, it's going to do this bubble copying bidirectional directions that we just looked at, and the single strands will fill in to make the double strands. And that process will continue, that process will continue, that process will continue, until we have an exact duplicate of the chromosome, the whole length of it, that will then be passed on to the daughter cell, the replicated cell. Okay.

So DNA synthesis in copying goes on in the cell all the time, natural process, and it follows that Watson-Crick base pairing law. That's required, A to T, C to G.

Okay. So then, as I said earlier, we have the 23 chromosomes, and in those chromosomes we have genes. There's approximately 20,000 genes. Each -- the strand -- scientists

consider both strands to be the gene. They orient in both directions. You remember the different directions that we talked about. They can orient in both directions. Both strands are part of the gene. And you may have intervening sequences between the genes. But what you have is just a series of A's, T's, C's and G's that are all mixed up.

And this might be I think helpful for Your Honor. When I talked about how it's an alphabet where you can make many, many words out of A, T, C and G, approximately once you get to 15 nucleotides, can sometimes be 17, can sometimes be 12, but once you get to that length and beyond that, there are no replicate words in the human genome.

So think about that. That means if you have a 20 nucleotide sequence, base pair sequence, based across the whole thing, it goes 20 nucleotides, that is highly unlikely to be found anywhere in that three billion sequence, except in that one place.

THE COURT: Is there a reason for that other than just mathematical probability?

MR. GAEDE: You just took the English major out of his realm, so I'm going to turn to Dr. Pribnow and have him answer that question.

DR. PRIBNOW: It's somewhat of a random chance. There are genes that are similar to other genes. There may be pieces of the genome where some sequences are more commonly

not -- not identical but close. And so if you were picking a primer, you'd probably want to make a larger primer or make a primer somewhere else, you know, rather than in that sequence if you wanted it to be unique. So on average, yeah, 15, 18, 20 long will tend to pick out a unique sequence. But, you know, the sequence of DNA in a human cell is not random; right? There are signals in there. There are things like telomeres on the ends where there are sequences that are repeated, you know, from one chromosome to another. There are things of that nature that would mean that some primers would not be highly specific, and so you take that into account.

MR. GAEDE: So you have the gene. And let's go through this a little bit more because I think this is important. The information contained within a gene is expressed -- you've probably seen these words, transcription, translation. Let me try to break those down a little bit more.

So first you have transcription. So I am speaking words to you. Those are English words. The court reporter is transcribing those words into text. But the word is the same. It's gone from a verbal word to a written word, transcription. Next is we'll talk about translation. I'm going to take that word, I'm going to translate it. So we're going to transcribe from DNA, which is a nucleic acid, to RNA. And you're going to make an exact copy, transcribed, what's called

pre-messenger RNA. You're going to be very familiar with the terms exons and introns and what happens. Then there's a splicing process at the mRNA. And the intron sequences are looped up, something in that nature, and then you have the messenger RNA because they're cut out.

So in this example here you have your genomic sequence. Of course it's going this way, it's going this way, but we're just focusing in on a part of this -- this entire continuous sequence on this part for this gene-x, and it will have the exon and the introns. An exact transcription, transcribed copy, will be made of what's called pre-messenger RNA. And then it will splice out those introns.

Why is that important? Because now we have to translate. We have to go from the language of nucleic acids to the language of amino acids, i.e., proteins.

THE COURT: Say that one more time.

MR. GAEDE: We have to go from the language of nucleic acids, DNA, RNA, to the language of amino acids, which are what proteins are made of. So first step transcribed, second step translate. And in the code exists the code for the specific amino acids. And I won't bother Your Honor with the techniques of how all that works. Just take it at face value that there's some redundancy. There may be more than one trip -- it's in triplets is how the language works. But there may be more than one for valine. Just take that at face

value. We don't need to go into the whole redundancy of the code.

THE COURT: Are there -- are there 60 some combinations --

MR. GAEDE: 64.

The COURT: -- and 20 --

MR. GAEDE: Yes. 20 amino acids, 64 triplets.

THE COURT: Right.

MR. GAEDE: Exactly. And so we translate now into proteins. Why? Because proteins are essentially what we are. They can be hormones. They can be enzymes. They can be structural. They can perform all sorts of functions in the body. And proteins are how the work in the body gets done. Our skin, made of proteins. We're basically to a large extent proteins. And the whole idea is that DNA is acting like the old, you know, hard disk storage drive. It's got the information. Then you're going to put it into RAM, which is kind of similar like mRNA because it's very temporary. There's all sorts of signals going on, but that's the concept. And then we're going to go into the proteins.

So DNA is -- some would think of it like a hard drive, long-term storage for the information necessary to make the proteins. And the proteins are really, for the most part, that's what gives life.

Okay. And think of it like a necklace with beads on it.

They actually are strung on by a process, and then it will kind of fold up in a certain way, and that helps give the protein its function. So you'll see it look here a lot and people will just show it as sort of a string that gets produced that then folds into a three dimensional confirmation, and that gives it part of its function.

So that's the basics of transcription into translation, all of which, of course, is being guided by the rule A to T, C to G, And that you need to also then -- you need to replicate that DNA in the daughter cells because they need to make the protein as well. So all that information has to continuously be passed on. The proteins are the large part of what make us.

So you've heard Mr. Jackson talk about mutations. And the reason why mutations are a problem is because it can mess up that translation process into the proteins where you put the wrong amino acid there or for some reason it's not there. It's not coded for. So the protein, the -- in this case the BRCA1 protein, will either have inserted the wrong amino acid or might even have one missing, and then it can't fold properly in that proper three dimensional confirmation, for example, and perform its function, which is to help the body protect itself from breast cancer, particularly in women who are more susceptible to breast cancer for various physiological reasons. So that's why these mutations are so

important because they cause an error in the process of going from the language of nucleic acids to the protein, which is the BRCA1 protein.

So here is just an example of that at a very high level. You have for example a single base pair change. So here we have the DNA and we have the A-T but underneath the arrow there, and then we'll have it in the mRNA. One technical detail. We have to be scientifically accurate here. You see a U there. You're probably wondering what the U is. The U is in fact -- in mRNA U is the same as T. It's just the way it is. Okay. And the same law though applies in that an A can only bind with a U.

So you change it, right, and now you have an amino acid change because it's the triplets that code for the particular amino acid and you have that change that's made. And now you have a mutation. You have a mutated protein. Something is wrong with that protein that's made by the body. And that then potentially can lead to cancer -- not always, but it can.

So that's why understanding mutations can be important. Because remember how we talked about, Your Honor, that there was some redundancy in the code. Some mutations don't matter. They're called benign; some do. And our sequences are not the same for all of us. There's differences in all of them. And these variations, they may have effect; they may not.

The COURT: Is there a -- is there any significance

for this case generally about why the introns are removed as part of the transcription process?

MR. GAEDE: Well, I think they are to this case in the next step that I'll get to when I talk about cDNA. That is why they're very important to this case. So the genomic DNA, the natural sequence, has the introns and the exons. That's DNA how it exists in your body with that sequence. So let me --

THE COURT: Well, it exists both ways, doesn't it, naturally?

MR. GAEDE: Well, no, it actually doesn't. So let me go back to here. Let me be real clear here because this is an important point for you to understand. In the body, remember, we've gone from DNA to RNA, not to DNA but to RNA, to proteins. Okay. All right. Now, in that RNA is all of the exons of the DNA with the introns removed, but that's an RNA sequence, not a DNA sequence.

I'm not going to go into this. I think it's fair to say that before the Supreme Court there was isolated DNA and cDNA. You can read the opinion for yourself. I'm going to explain the difference between the two.

So what are your sources of isolated DNA? One, natural, you can extract it --

THE COURT: Well, before we get into this, let me ask you this question. Is there some accepted definition of

this term isolated DNA within the scientific community or do scientists vary in their views about that?

MR. GAEDE: To the best of my knowledge, and I would certainly defer to Dr. Pribnow on that, to the best of my knowledge it encompasses a piece of DNA that has been isolated in some form or fashion and sitting in a test tube. And so it can be made synthetically. It can be made by bacteria. It can be taken from the human. But isolated DNA to my understanding, and I would say as expressed in their patents too, includes all different ways to make it.

THE COURT: Mr. Mangum, do you agree with that or is there -- this has been the subject of some discussion, of course, in the legal proceedings, and there may be legal definitions that are ascribed to this. I'm asking as a matter of science if there's some general consensus.

MR. MANGUM: We disagree with the statement that suggests that there's some in science. I mean -- and Your Honor has appropriately pointed it out. There's issues with regard to claim interpretation, which are issues about how -- what that means in the patent. There's then interpretation when one reads the Supreme Court's decision what does the Supreme Court and specifically Justice Thomas mean when he uses the word isolate versus extract versus everything else. No, we don't concede that there is a scientific understanding of the term isolated DNA. It's an issue of claim construction

on one side and an issue of interpreting the Court's opinion on the other.

The COURT: All right, thank you.

Mr. Gaede proceed. I'm going to assume that for our purposes today you're providing -- you're using terminology in an illustrative and demonstrative fashion.

MR. GAEDE: Correct. I understand the point of contention. I obviously don't agree with it. So the point being that when you isolate it, either -- your source, either you make it chemically or you make it in a bacteria for example, or you take it from the human, the segment, the isolated DNA segment, is indistinguishable because it must follow -- it is DNA and it must follow the Watson-Crick natural law base pairing rule.

And remember when we talked about chemical structure at the beginning where we showed it? Again, you have the backbone. Same in all three. You have then the nucleotides that are forming the base pairs. Each has it own chemical structure. A has its chemical structure, T has its, C has it, G has it. And then of course they hybridize or bind according to the hydrogen bond according to the principle that A can only bind T, C only to G.

THE COURT: Freeze that slide for a moment, will you?

Mr. Mangum, is there dispute in this case that isolated

DNA segments, whether they appear naturally, other than cloned or chemically synthesized, if done correctly are indistinguishable in each instance?

MR. MANGUM: Well, I think, Your Honor, if the question is, and as I understand the question, is if you look at a particular segment and you have a particular sequence within that segment, whether that segment was created -- was extracted from the body or whether that segment was synthesized in the lab, does it have the same sequence of molecules and therefore have the same chemical property? Yes. But when you look at it from the standpoint of is it the same molecule, that little segment, when it's connected with all of the rest of the segments? No.

I mean if you pull out that segment, it's -- it has a different chemical property than it did when it was in the body when it was connected with others. Have I stated the science correctly?

DR. ROA: Yes.

THE COURT: Let me restate the question back to you and see if we understand each other. I think we all agree the nucleotide sequence will be the same.

MR. MANGUM: Correct.

THE COURT: Chemically, physically will there be something that will distinguish a DNA segment that's found in natural DNA from one for example that is chemically

synthesized?

MR. MANGUM: If it is --

THE COURT: Just a discrete segment.

MR. MANGUM: A discrete segment, no.

THE COURT: All right.

MR. MANGUM: Inside the body, yes, outside the body, no.

THE COURT: I think I understand.

MR. JACKSON: I think the point is that the -- the sequence will be the same in that region let's say. The larger molecule will have a particular region in which the sequence is the same. The smaller molecule will have a sequence that is the same. The chemical properties of those two different molecules will be different because of their different size and the extraneous sequence that's in that other one. But along that portion --

The Court: I think I understand Myriad's position. I just wanted to see where -- trying to vet out where we have agreement and disagreement.

Thank you, Mr. Gaede. Go ahead.

MR. GAEDE: Okay. And so isolated DNA follows the ordering of the natural DNA sequence. And that's true whether it's a single strand of primer, plenty of examples we'll show you in that, also true if it's in a double-stranded form. It's following that sequence. Yes, I would agree that this is

not that as a sequence. But there's no question --

THE COURT: Well, we're going to save that discussion for another day, but let's go ahead.

MR. GAEDE: All right, sorry.

THE COURT: I'm going to allow me to dabble in that but not the two of you.

MR. GAEDE: Okay. So let's just make sure on cDNA we understand. You asked the question is that found in the genomic DNA. And the answer is for cDNA, no, it's not in most instances, and here is why.

So, again, remember you can go back to your exon, intron, exon, intron in the DNA sequence. You then are going to transcribe into mRNA. Those introns are going to be cut out. Now you have the mRNA RNA sequence. And then scientists use something called reverse transcription. Think about that, reverse transcribing, I'm going back to the DNA language from the RNA language that I'm in right now, or I'm going to transcribe it from that nucleic acid to one other, and I'll make a DNA. Okay. So that cDNA with those three exons is not normally found in the body as a contiguous sequence because of the sequence that goes exon, intron, exon, intron, exon. And so that's why you see those parts here in this other slide, same concept, exon, exon, exon going into the cDNA.

In some circumstances though you can make a cDNA that would be indistinguishable from the genomic DNA. So, for

example, there are some where there just isn't an intron in between. You have the mRNA coming down. You're making then -- and the DNA would be an exact copy of what's up there. Also you could just take a short piece of mRNA, reverse transcribe that, and that DNA sequence would reflect exactly what is in exon 3 for example. That's the point here about some could be indistinguishable cDNA made in the laboratory from a naturally occurring DNA sequence.

Now, again, I put this in just to let you know the word primer is in there. There's been obviously a lot of discussion about primers. But I think what's important about primers is this. And you heard in their presentation to you the primers bind -- this is in their video -- the primers bind or anneal to the location that is precisely complementary to the nucleotide sequence of the primer. Sounds like a lot of gobbledygook to me. Let me try to explain what that means because that's important.

THE COURT: Let's try to be free of argument as we're --

MR. GAEDE: No. I wasn't trying to actually do that. I was actually trying to say that to get away from the terminology because the biggest burden I think the parties face and the Court faces is the terminology, what does that mean. So I apologize. I did not mean it to sound that way.

Here is what I mean. When it says perfectly

complementary following that natural law, Watson-Crick base pairing, lines up exactly. So how does that work?

THE COURT: Well, by definition I think, right, I mean that's the purpose.

MR. GAEDE: Exactly. So you have an example here. You have the primer. You have the two strands of the genomic DNA, and in it comes and binds exactly, perfectly complementary.

THE COURT: How are you using that word complementary when you say that just then?

MR. GAEDE: It means C-G, C-G, T-A, G-C.

THE COURT: There's a term of art, complementary DNA, right, cDNA?

MR. GAEDE: Yes.

THE COURT: I'm just wondering if you're using it in this context when --

MR. GAEDE: No, not at all. Complementary just speaks to the issue of the base pairs being able to bind across each other.

The COURT: I just want to make sure we're on the same page.

MR. GAEDE: You're right. This is another example. This is from Mr. Roa's declaration. Again, you see the example of matching up perfect complementary for the primers to the natural genomic sequence.

THE COURT: This would have been -- maybe I should have put this question to Mr. Jackson during his presentation. Will you go back a slide. This was depicted -- this is similar to a depiction in Mr. Jackson's slide. It's headed in the direction of three prime on the top and five -- well, three -- says reverse prime on the bottom. When does it stop? Is there a primer set both at the beginning and the end of the sequence on both strands?

MR. GAEDE: No, no. It just extends out.

DR. PRIBNOW: To the end of the template strand.

MR. GAEDE: To the end of the template.

THE COURT: The template strand?

DR. PRIBNOW: So if you back up one more slide, the primer is actually operating on a single-stranded DNA like you see on the bottom. And so the priming reaction just gets the polymerisation started on the DNA (inaudible), nucleotides until it hits the terminal nucleotide and completes the chain and you have a double-stranded molecule.

THE COURT: And in the opposite direction --

DR. PRIBNOW: Same thing happens in the other direction, just copying information on the strand that's being used as a template, uh-huh.

THE COURT: So the entire strand -- none of you like this word, but I'm going to use it for my own lack of sophistication about this. The entire strand is copied in

that process, but one portion of it is copied twice; is that right?

MR. GAEDE: Yeah. I think -- let me go to this slide. I think this might help a little bit because I think this is the point that Mr. Jackson was making.

THE COURT: Actually, let me restate that. Half of each strand is copied -- no, that's not right either. I think I understand.

DR. PRIBNOW: You get two separate strands, each one is copied, one from one end to the other. It's always in the five prime to three prime direction, which is why one goes across in one direction and one in the other direction, the way that they're drawn in a presentation like this.

THE COURT: And one portion of the original strand ends up being duplicated completely because it's copied on both -- once you separate the two, it's copied both the bottom part and the top part. They're inverse to each other in between the two markers. Do I have this wrong?

DR. PRIBNOW: Yeah, they're inverse to each other so you end up with two identical copies of what you started with before you separated the strands.

The COURT: But only for a portion of the strand that we're talking about, no?

DR. PRIBNOW: Yes, I suppose, right. If you're talking about a longer DNA that you began with with the primer

sitting down. I think you're alluding to the PCR process now in a sense.

THE COURT: Yes.

DR. PRIBNOW: So that's actually going to be addressed, well, soon.

MR. GAEDE: So this is --

THE COURT: We'll get back to Mr. Jackson. Go ahead.

MR. GAEDE: Well, this is the point that Mr. Jackson was making. Remember, you take the genomic DNA. You're going to break it up into all sorts of pieces. The primers, which are perfectly complementary to the DNA sequence, are then going to -- they'll be separated, the strands, they will then come in and bind, they'll start the PCR analysis.

Mr. Jackson's point was that, well, technically because you've broken the DNA, the genomic DNA up into chunks, and then we're going to make copies of a smaller portion of that chunk, that the ends are different. But there's no question, and I think we have agreement on this, that the nucleotides that are being copied are being copied faithfully and accurately, because the whole point of testing is to make accurate copies. Because if we don't make accurate copies, very terrible medical decisions will be made. A woman could perform a double mastectomy or hysterectomy based upon false information. So it depends upon the fidelity of the copies.

Let's go back to ours. So, again, the primers come in. They could either be at the end or they could be somewhere further in. They separate. The primers, of course, perfectly complementary to the DNA. They bind. Copy during that process, similar to what you saw in the chromosome, same thing, going in both directions because it harnesses that natural process, and then you have a copy made of that section.

THE COURT: Will you go back to slide 59.

MR. GAEDE: Yeah. Your Honor, I don't know if you're looking at our slides. They may be off one because we put in that other slide that had the depiction from Mr. Roa's, if you're looking at ours.

THE COURT: I wasn't, but thank you.

MR. GAEDE: Happy to give you the corrected set that has that one example from Mr. Roa's declaration as well. So the PCR happens and the copies of the natural DNA sequence are made, identical copies. And then it will cycle through this process called PCR, which was invented I believe in 1985, and the inventor was awarded the Nobel Prize for the discovery.

And this right here is just a summary overview of how copies of a particular sequence in the genomic sequence is made. One way to think of it, Your Honor, is if I took this patent here and I took a page out of it and I made copies of it, that's what we're doing.

THE COURT: So this is where I'm getting hung up. Let's look at this slide for a moment. If you look at the left-hand column, and come up from the -- to the second depiction from the bottom on the left. Neither your depiction nor the one we saw earlier continues the strands out -- on the top portion it would be to the right and on the bottom portion to the left. But we're starting -- we're starting the PCR process where we've placed the primers, and the DNA strand continues beyond where the primer was placed, and there's just nothing being copied there. Is that what happens?

DR. PRIBNOW: So you're being astute in your observation here. There is a -- something is a little bit misleading. For the first round the primer will indeed prime a reaction that goes way off in the other direction and who knows where, at the end of fragment that's copying, but now it has a fixed end on the right. Okay. Similarly, if you go off and copy in the other direction, that will have a fixed end on the left even though it went off in the other direction. When those are separated and copied, okay, now the -- gosh -- the one that has a fixed end on the left now is copied from the right and now the enzyme just runs to the end and stops. So that's where you get your stops.

And I apologize, we apologize that we sort of omitted that detail thinking that it would get confusing, but you're absolutely right that it ought to be there for the sake of

completion to show you what happens. And then those longer strands just stay there. They're in the reaction but eventually there are two of them --

The COURT: As Mr. Jackson said --

DR. PRIBNOW: -- there are a billion other copies.

THE COURT: As Mr. Jackson said, they become vastly outnumbered for this reason because that's the portion and it continues to be replicated.

DR. PRIBNOW: Correct.

The COURT: Then I understood it better than I thought I did.

MR. GAEDE: And then you make identical copies of the sequence of the genomic DNA of a portion of that sequence. Again, we put this in here just so that -- talk about sequencing. You know, I think the bottom line -- I was listening to Mr. Jackson here when he was talking about how each one keeps adding one on during the next-generation sequencing process, all you're doing is just following the natural sequence that exists. And I think that's the important thing when you think about sequencing which has existed since 1977 with Sanger sequencing. There's also another one -- I'm not going to bore you with the details -- it's called Maxam-Gilbert. Turns out that Dr. Pribnow actually was in Dr. Gilbert's lab in 1975 and a year later it was invented in Dr. Gilbert's laboratory.

It lays out and it's able for us to be able to read. Once we have sufficient material, copies of the DNA sequence, we then have to be able to read it, and we do that through Sanger sequencing. We do that through old technique, Maxam-Gilbert. We can do it through Next-Gen. But what we're essentially doing is again harnessing the Watson-Crick base pairing that starts again with a primer type substance that again reflects exactly the sequence. And so you just line it up, and then you'll be able to read that sequence.

And of course the whole point is we have to be able to faithfully read the sequence in order to understand whether there has been a mutation in the sequence or whether it's the wild-type sequence or whether if there is a mutation is it benign, is it potentially a problem.

So that's why fidelity of the whole process depends upon absolute replication and absolute fidelity in terms of the reading of the sequence that are generated to, not deduce -- I think that word -- we object to that word because I really think that is misleading and understates the issue. It's important to get it right, and the process depends upon replication. I agree we don't have -- we don't have a microscope that can yet read the sequence directly. That is true.

THE COURT: I actually think you're both saying the same thing in that respect. I mean it's deductive logic that

allows you to infer what's attached. It's the same process you're describing. You're -- both sides are saying the same thing. You're relying on the Watson-Crick principle to know what the strand is by virtue of -- by -- of necessity because of what attaches to it.

MR. GAEDE: Correct. And then you might have -- in that last claim you might have an allele, a specific type. That's a fancy word for a specific sequence. You may have a mutant. So you have your hybridization using again sort of -- in this case it's called a probe but it's very similar. In other words, it's a single-stranded DNA structure that's designed to be perfectly complementary to the opposing strand. And here you have two different sequences that have been replicated and now we're going to probe them.

And you can see there's a mismatch because C can't bind to T. So you're not going to get a stable probe. Unlike over here you have a stable one because you have a perfect complementary going across the entire sequence, the contiguous sequence. That segment of DNA has a contiguous sequence.

We also -- he also talked about large changes in genomic DNA. I think we would disagree. We can, of course, detect these larger changes in the DNA sequence by Sanger sequencing. You're just going to stop. You keep sequencing parts and then for some reason you hit, if you will, a hole, a blank stop. That would infer you to lead -- to understand that there's

been a deletion.

Right? Have I got that right?

DR. PRIBNOW: Well, you can adjust that statement a little bit and say you find the sequence suddenly veers off from what you expected. It goes into different sequence, right, because the DNA molecule that's being copied is a continuous sequence of something. So when you copy it and -- in order to sequence, or when you PCR across that interval and then sequence the PCR, you discover you get the sequence you expect and suddenly it goes into something else.

Now, if you know a lot of the distal sequence, you can take the sequence on the other half of your PCR product and ask where does it occur? And if it occurs a thousand base pairs away, then chances are you have just detected a deletion of a thousand base pairs in the DNA sequence. Do you understand what I'm saying?

THE COURT: I do.

DR. PRIBNOW: So Sanger works very nicely actually to look at deletions, to find deletions. It may not be the best in all cases but it certainly works.

THE COURT: My impression is these are different tools for researchers to use for different things.

MR. GAEDE: Correct. I'm not going to go into this too much, the whole microchip. You just have a bunch of specific probes, as Mr. Jackson said. Each will target a

specific area along that gene sequence, and if you have a big deletion, there won't be that complementation happening and so therefore it won't be detected. And you say, ah, that wasn't detected because I know that probe is designed to hybridize perfectly to that particular sequence of the DNA.

And go through it -- remember, you could have the situation, because we have two chromosomes, right, so we could have for example a deletion in one but not in the other. And so in that case you would say, ah, I've got a 50 percent less amount. And I would say, hum, okay, so what's going on in this human is on one chromosome where the BRCA gene is I have a large deletion. On the other one where the BRCA gene also is, I don't. So maybe that means that that particular human will produce less BRCA protein, may or may not.

And I think what helped me a lot to understand it is this, and it goes back to maybe some basic high school biology that you may have had many years ago and it may be coming back. You remember that when you have a mother and a father, each contributes one chromosome, and then they combine together to make the pair of chromosomes.

Now, in order to do that, the mother and the father, of course, they have pairs of the chromosomes in the cell. To make the sex cell, they have to make a cell that just has the one chromosome in it. And during that process of that division where you have the double -- the two chromosomes that

are together and one is being if you will just broken off and put into a single sex cell -- I'm sure I'm being way over simplify -- simple enough but it's an important concept. During that process pieces of DNA can go back and forth between the two chromosomes. You can have what's called recombining.

And so during that process a piece of DNA up here for example could go over here and this can go over here. And that gets important because from that you can start to detect through hereditary, which I'm about to go into, traits, and recombining and this concept that you'll hear of markers.

So this slide is a little bit premature in that it doesn't show that actual division happening or separation happening between the -- in the mother and the father where each one is going the donate one, but during that process in particular DNA can go back and forth.

Did I get that right?

DR. PRIBNOW: Yeah, recombination occurs during miosis which is when the (inaudible) are produced.

MR. GAEDE: That leads you to the concept of markers. Because remember, Your Honor, we have three billion base pairs, six billion nucleotides in this long sequence, and trying to find out where a gene is is literally looking for a needle in a haystack.

And so what they look for are what are called markers.

Is it on chromosome 5? Is it on chromosome 17? Is it on 19? They don't know. And you need to at least know in general what chromosome first before you then begin to use other techniques to zero in on what is the DNA sequence that is that particular gene in that chromosome.

So this is a pretty simple illustration, but geneticists use this concept of markers to begin to hone in on where the gene is. And in this case here it might be a little bit too complicated, but stick with me for a second because I think it -- I think it helps.

So you have an affected person in this case, someone who is more susceptible to cancer because they have a problem and they have cancer in their family with respect to the BRCA1 gene. And you have other markers that are passed on between the father and the mother, because remember each contributes that chromosome. Then they combine and you can have different combinations for the children. So you're looking for a marker.

So you're saying here you know that mother doesn't have this particular marker on her chromosome 5 but you know she's got a marker on chromosome 17 and in this case 19. You then start to look at the children. And you know this mother has breast cancer. And, again, this is much simplified form, but it gets passed on.

So you say, hum, okay, well, I see now if someone has

breast cancer, the females there in the circle, that must be on chromosome 17. So I've got a marker now, this concept of a marker, that's tied to the -- what they call phenotype, i.e., the problem, if you will, or could be blue eyes, could be green eyes, could be brown eyes, but some expression. And that's again very oversimplified but what's going on is geneticists are using this concept of markers, and they're using then genetics and the issue of recombination and understanding that that happens.

And the principle is in the long chromosomal DNA, the closer the marker is to the gene itself, the less likely it's going to recombine away from that gene, because pieces go back and forth. And so if it's real close, you then start to see that, okay, that's got to be where the gene is located because it's not somewhere else.

Let me give you an example of that. This is in the patent, and what geneticists do is they identify a series of markers. And here you see a section, and it's honing in on this part of the chromosome. Because, again, if there's going to be recombination, the marker is going to tend to go with the gene if it's really close. If it's not, it will tend not to go with the gene. And so using this process of markers in genetics, scientists can begin to hone in on where the gene is.

And that's where you're going to hear in this case

terminology around markers, and they are used by geneticists to locate a location of the gene, likely where it is, and allow them to hone in as to where it is in that haystack by using markers, i.e., pieces of colored straw that are in that haystack to help them get there.

And I'm not going to get into this too much. It's in the patent. But what do they do in essence, you have a piece, here this piece 17q 12 to 21 of this longer human chromosome, and then through a process of delineating it down further and further you will then further hone into the gene. And you'll hear this terminology, I apologize for it in this case, you're going to hear yeast artificial chromosomes, larger sections being copied, then you're going to hear smaller subclones, smaller pieces, cosmids. And then you're going to look for some mRNA as one technique, say is there a gene there, is there not?

And through that you're going -- that iterative process you're going to hone in on where the gene is within that longer sequence. And those are methods that geneticists used at the time that the patent applications were filed.

Now, with that --

THE COURT: The same techniques that are used today?

MR. GAEDE: I believe many of the same techniques are used today. I'm sure there are additional techniques that are used today as well, yeah.

THE COURT: Thank you, Mr. Gaede. Anything else?

MR. GAEDE: No. I think that's it, Your Honor.

THE COURT: Mr. Mangum, anything you or Mr. Jackson would like to add or clarify? Would you like a recess for a few minutes and --

MR. JACKSON: If we could.

MR. MANGUM: Why don't we do that. I think that will help us winnow down what's important.

THE COURT: Why don't we do that.

And then, Mr. Gaede, we'll hear one more time from your side if it's necessary as well and then we'll wrap this up.

Thank you. We'll be in recess for about 10 minutes.

(recess from 3:57 PM until 4:19 PM)

THE COURT: All right. Mr. Mangum, before we hear from you, this gives me just a little bit of pause, but I'd like to be thinking about some of this between now and the time of our injunction so I'm going to walk up to the pool and dip my toe, and I hope neither of you will push us in the pool.

A couple of questions. Let me put them to Mr. Jackson to start, anyone on your side, and then we'll hear from the other side, and then I'll allow both sides an opportunity to sort of wind up and address anything you think we need to touch on.

At times today I know we talked briefly about synthesized DNA. I'm not sure if we talked about purified DNA. Would you

take a moment and talk about those.

MR. JACKSON: So by purified DNA, as I hear that word or that term, I would take that to mean DNA that has been purified out of a -- say a natural source, such as a patient's cells. Is that where -- what you're asking about?

THE COURT: Maybe I should have started with this question. Is purified DNA a term of art among scientists in this field? Does it mean something specific? Is there an agreed upon meaning of that phrase?

MR. JACKSON: I'd say probably yes. I would say if you said to a scientist I've got a sample of human cells and I want to get some purified DNA, what does that mean, I think the scientist could tell you what that means. Yeah, I think so.

THE COURT: And what would the scientist say?

MR. JACKSON: I think the scientist would say it's DNA extracted out of those cells. The cells would be broken open, the DNA would be pulled out of wherever they were naturally, and separated away from the natural surrounding molecules, proteins, whatever else, and then into -- purified to some degree and then put into a different solution, a different test tube let's say.

THE COURT: Process of isolating say the DNA strand, the double helix for -- maybe I'm oversimplifying -- pulling that away from the other parts that are found in the nucleus

of the cell?

MR. JACKSON: Yeah. There are processes for doing that.

THE COURT: All right. And that's what you think it means to purify DNA?

MR. JACKSON: Yes.

THE COURT: And what is synthesized DNA? Is there a common understanding of that phrase among scientists do you think?

MR. JACKSON: Probably less so, probably less standard.

THE COURT: What's your view about what that phrase means?

MR. JACKSON: When I hear the phrase synthesized DNA, I think of DNA generated through some non-natural process. Now, the word synthesis is often applied to natural processes, for example, DNA replication we heard about. You can say that the DNA Polymerase synthesizes the DNA molecule. That is true.

But when I hear the term synthesized DNA, to me it implies DNA produced in some non-natural process, such as PCR for a much larger piece. If you've got a smaller piece for say a primer, you could do that in a separate oligo -- they call it an oligo synthesis machine. It's a machine that just catalyzes the chemical reaction to add one onto the next.

THE COURT: What is the -- what does an amplicon refer to?

MR. JACKSON: So an amplicon -- remember when we were talking about PCR and we talked about the pair of primers that are used in PCR, one anneals to one template strand and the other one anneals to the other, and they prime that synthesis reaction? Then they separate and you notice that after a couple cycles, the molecules tend to be bounded by that -- those primers; right? Those molecules that are bounded by the primers are the amplicons. It's the set of all of those molecules having that sequence bounded by the primers.

THE COURT: Is there a common understanding do you think among scientists about what the term pseudogene refers to?

MR. JACKSON: Yes.

The COURT: What is that?

MR. JACKSON: And, by the way, I think that amplicon is also a pretty standard term, very standard term. I think you get pretty much that exact same answer. So as far as pseudogenes, a pseudogene is a portion of genomic DNA that resembles an mRNA in the sense that it's a portion of DNA in just the natural genome that may have introns removed. Because what happened is we've been living around here for a long time, humans, and we've been infected by viruses as we've

gone along, and certain viruses perform this reverse transcription Mr. Gaede talked about.

Normally within humans it's one directional, DNA, RNA, Protein. But viruses have the molecular machinery to go the reverse, to go from RNA to DNA. And so when they infect our cells over these eons, they have just by chance that machinery from the virus reverse transcribe an MRNA into a DNA, and then that DNA got reinserted into the genome. And that becomes what we call a pseudogene. Those can sometimes themselves be back transcribed into a partial mRNA.

It's very rare for a pseudogene to be the entire gene, especially for a larger gene like let's say BRCA1 or BRCA2. They're very large. That typically doesn't happen because this is just -- it's a -- it's a chance occurrence inside somebody's body.

So, anyway, sorry, that was a very long explanation, but that's what a pseudogene is.

THE COURT: And that typically refers to the entire gene, not just some segment of the DNA that makes it a part of the gene?

MR. JACKSON: Well, again it will be -- it will -- for a small gene it could be a reverse transcription of the entire thing. That happens sometimes. Now, there's usually errors in there. It won't be an exact copy because the viral machinery doesn't work that well. But for larger genes you

would probably -- I don't know that you would ever see a pseudogene big enough to cover a large gene.

DR. ROA: You can't have pseudogenes that only cover a portion of the real gene. Usually pseudogenes usually are not functional. You can also have pseudogenes in some cases that do have some introns (inaudible).

(The reporter asked for clarification)

THE COURT: You can also have some pseudogenes that have introns.

MR. JACKSON: Yes. Because the virus caught the mRNA before it got spliced.

THE COURT: I gather it's an unusual condition. It's not something that's -- most of us as humans are not carrying around pseudogenes or are we?

MR. JACKSON: No, no. I mean most humans will have the same set of pseudogenes more or less. Now, there will be more variation between us. Like my pseudogene for a particular gene, let's say the PTEN gene, which is one I'm very familiar with, my sequence might be very different from yours, your pseudogene PTEN, because it's not functional and there's no pressure to keep it the same; right?

There's selective pressure to not change a gene that's functional because it could cause a bad gene. If there's a change in that gene, it could cause disease; right? Pseudogenes aren't functional, as Dr. Roa said, so they can

change all over the place.

The Court: All right, thank you. I'll save the last question for the lawyers I think, but Mr. Gaede let me let you first respond to that. Any disagreement with that -- with those answers with respect to understanding of what purified -- what purified DNA is?

MR. GAEDE: Actually I do, because purified just simply means purified, i.e., it's in a mixture of something else. You purify it out, and you can do that in the laboratory. It can be purified away from the cell. You could have a mixture of materials in a test tube and you purify the DNA out.

So I would -- I would not agree that purified DNA stands for just simply DNA that is purified from the cell. I don't think one of ordinary skill in the art would understand that term encompasses just that act of purification. There can be many, many different types of acts of purification around purified DNA. But I would agree that one act of purifying DNA would be to extract the DNA from the cell and separate it from the proteins and other associated material.

THE COURT: All right. What about synthesized DNA? Anything you would add to Mr. Jackson's explanation of that phrase?

MR. GAEDE: I would add the word chemical to it. Synthesis can, as we saw, can be natural synthesis. It can be

in a bacteria. It could be chemically synthesized. It could be a combination of harnessing natural processes, such as in PCR because you're using that natural process.

So I wouldn't necessarily say that the word synthesis in and of itself is descriptive. It is more -- chemical synthesis is typically more descriptive of the process of chemically synthesizing DNA.

THE COURT: Well, contrasting that from other forms of synthesized DNA is your point?

MR. GAEDE: Correct.

THE COURT: All right. A more specific application?

MR. GAEDE: Correct.

THE COURT: And amplicon, I think I share Dr. Jackson's -- is it Doctor?

MR. JACKSON: Mister.

THE COURT: I tried to give you a promotion today. Amplicon is a commonly understood phrase. It's what you described. Do you agree with that?

MR. GAEDE: I agree that it's a copy of the target DNA. That can be genomic DNA. That could be a synthetic sequence that is made by man only. You can amplify various things, but it's a copy of the target DNA that is being copied. In this case we've been talking about genomic DNA, the DNA sequence found in the genome.

THE COURT: Through PCR?

MR. GAEDE: Yes.

THE COURT: All right. Pseudogenes?

MR. GAEDE: You got me on my knowledge there. I don't know if Dr. Pribnow has anything to add to that. I'm not as familiar with that subject matter, other than I do agree we have viruses. We have that process -- it does happen in our body and I know that parts of it can recombine into our genome. But that's stretching my limits so I'm going to ask Dr. Pribnow to --

DR. PRIBNOW: Well, it's stretching my limits a little bit too it turns out. I don't know that much about pseudogenes. But the descriptions that I heard to my knowledge sounded reasonably accurate, so --

THE COURT: All right.

MR. GAEDE: And at a high level I don't have a lot of problem with Mr. Jackson characterizing it.

THE COURT: My last question. I'll put it first to you, Mr. Gaede, and then, Mr. Mangum, I'll invite you to respond. What do the defendants contend that the phrase isolated DNA refers to?

MR. GAEDE: It refers to a DNA segment that has been either isolated from natural DNA, recombinantly made or chemically synthesized, and that has in the case of the Supreme Court's decision has a contiguous sequence that corresponds to a portion of a naturally occurring sequence.

THE COURT: Well, does that phrase, isolated DNA, have some discrete meaning among scientists separate from what lawyers and judges have done to it?

MR. GAEDE: Well, I do believe it does in the concept that in the genomic DNA you have the DNA existing in the chromosomes in the cell, and I don't think anyone would look at that as a scientist, based on my years of practicing in this area, and say that's isolated DNA.

Do you agree with that Dr. Pribnow?

DR. PRIBNOW: Yeah.

MR. GAEDE: Now, obviously once you have isolated a DNA sequence, a segment of DNA, that is an isolated DNA. How it is made in my understanding is not important. It's the fact of isolation that's what's important.

THE COURT: Where does that understanding come from, the understanding you just described? From where does that derive?

MR. GAEDE: Two places. First I believe that's terminology that is used in the field. Secondly, that is terminology that has been used since the early 1980's in the patent law.

THE COURT: Is there a distinction that you would draw between isolated DNA and purified DNA?

MR. GAEDE: Again, going back to the purified issue that we talked about, isolated DNA simply refers to the DNA

structure that has been isolated and can be made from a number of different ways. The question is what is that isolated DNA? What is that composition? What is that product? And that is the question that needs to be answered for what is isolated DNA.

THE COURT: All right. Mr. Mangum, do you care to address that or have someone on your side address this issue of -- I'm jumping the gun just a little bit on you here. We'll be receiving some briefing that will relate to this, but I'd like to digest it a little bit between now and then.

MR. MANGUM: Okay. And I come back to what I said before. First of all, isolated DNA is not a term of art, not something that's commonly understood, you know, in the field as being one and only one thing as opposed to kind of a broad thing that might have some genus that would have some species underneath it.

Where I think it comes into play in this case, and where it comes into play in the briefing that we'll be pleased to be able to address, is that there -- and it's what I alluded to earlier. Those are terms -- isolated DNA is a term used in some of the claims of the patent. And with regard to that term, using claim interpretation principles and looking at that term as it's used in the specification, there is a proper claim construction for that term.

That does not mean that you can then take that term as it

was used in the patents and say, well, anytime anybody uses the word or the phrase isolated DNA they're talking about that isolated DNA as used in the patent, as construed by Judge Sweet, as dealt with by the courts. And I think very importantly, reading and parsing, as we're going to need to do in great detail on September 11th the Supreme Court's decision, there are statements in the Supreme Court's decision where it is clear that the court and Justice Thomas is using the term isolate synonymously with the word extract.

And so when the court is talking about isolating, the Court is talking about -- in my view, and this will be our argument -- is talking about DNA that is extracted from the body, and then he contrasts that and uses other terms when he's talking about chemically synthesized DNA or creation of DNA.

Anything to add to that?

MR. JACKSON: No.

MR. MANGUM: And then Mr. Jackson just had -- I certainly will answer whatever questions the court has -- just two points in rebuttal to Mr. Gaede in terms of the general presentation.

THE COURT: All right, thank you. Well, I'll look forward to our discussion about our claims and terms on September 11th. This is helpful.

Mr. Jackson, a general response to the scientific

portion.

MR. JACKSON: Just two points, Your Honor, I just wanted to emphasize. We talked a lot about primers and PCR synthesis, PCR reactions. And one point that I wanted to emphasize there is the way that the primers work in tandem as pairs, primer pairs. For this type of a PCR reaction you need two pairs that will work together to result in that exponential amplification from PCR. So it's an important thing to remember. I hope that that came across well in the presentation.

The Court: When you say pair, you're talking about the fact that there are of necessity two of them, but they're -- they're not identical. They're different because they attach at different --

MR. JACKSON: Correct. Exactly, correct, yes.

The Court: All right.

MR. JACKSON: And another point we -- I think we probably belabored this point a lot, but I'd like to come back to it, is this issue of segments versus whole -- segment DNA versus whole, whether an amplicon is the same as the larger DNA molecule that was used to generate it. Just a couple points on that.

I emphasized in my presentation or I pointed out that it's a different molecule; right? It doesn't have that entire sequence that the original DNA did, but as we I think pretty

well fleshed out, a portion of it does in fact align, a portion -- the amplicon molecule, let's say, that PCR synthesized molecule, will share sequence with that larger molecule. So we all kind of agree I think on that.

But the -- a couple points to remember are that they are different molecules. That the amplicon molecule is chemically synthesized rather than extracted out of the cell. And that, like in the instance of a primer let's say, while it shares certain sequence with that original DNA, it has different chemical properties, and it was designed to have particular properties.

Mr. Gaede talked quite a bit about information. He used the analogy of the hard disk and the computer. Analogies can sometimes be helpful. In that analogy I would say that a primer is more like a piece, a piece that you've created that can be used with say the hard disk; right? Whereas the hard disk might carry a bunch of information, that little tool, that little primer, really doesn't from a genetic perspective, from a biological genetic perspective.

You know, Mr. Gaede emphasized the informational aspects of DNA. I don't see much information in a PCR primer. It's not going to tell you -- it won't encode a protein; right? It won't -- it probably won't be enframed to be able to encode a protein. It's a tool used in a laboratory to generate a molecule. So I kind of wanted to emphasize that.

And the design of that primer is -- we heard a lot about natural laws and Watson-Crick base pairing. Certainly when someone is designing a primer and they're looking at their target sequence and trying to decide what's this primer going to look like, they definitely consult the natural chemical laws underlying that base pairing, and they apply it. They say here is what I know about base pairing, about the way that these chemicals interact. Here's what I know about my target sequence. And these are important things to know, especially the target sequence; right? I'm going to apply that in this way and design this primer. And that's -- that's how they do it. They -- yeah. That's how we do it.

That's it. Did you have questions?

The Court: One I think on this point. Maybe it's an imperfect analogy but it's simple so I like it. Let's think again about a chain. I think you're the one who introduced this idea. Let's think about different colored links representing our A's and T's and C's and G's. We have a 10 foot segment and we want to create an exact copy of the segment that runs from the fifth foot to the sixth foot in the chain. We can do that by binding colored links and assembling them in the same order. But in genetics and through PCR will there be something else that will be different about that one foot segment? For example, I'm wondering about will the links on the end, are they closed in some fashion? Is there

something physiologically different about the amplicon?

MR. JACKSON: In some applications they can be. For instance, when Myriad itself does its Sanger sequencing, the primers have chemical labels attached to the end let's say. And so then they perform their amplification, this synthesis reaction and the resulting molecule then has this chemical modification on the end. That's what allows us to ultimately see what the sequence is going to be. So it depends on the application. It doesn't have to be chemically different.

THE COURT: Is that something that prevents molecules from bonding on the other side of the primer?

MR. JACKSON: The directionality of the molecule would already prevent that. Remember the five prime to three prime?

THE COURT: Yeah.

MR. JACKSON: So this label is going to be on the five prime end and you can't add. That's how it works under chemistry and biochemistry. It cannot -- you can't add in that direction. So that's true. So you put the label there on the end.

THE COURT: Okay, thank you.

Mr. Gaede, anything more you wish to add?

MR. GAEDE: No, Your Honor. I think we've talked about the issues in that respect. I think it was a little argumentative at the end, but I think we're done. I do have a

few questions if the Court would entertain them about the structure of the hearing.

THE COURT: Well, let's talk about that and clean up any housekeeping issues we have to address. What's on your mind?

MR. GAEDE: So, first of all, we have the 11th blocked out, and then the morning of the 12th. We have obviously submitted a number of declarations to make the record. You have also said that if a witness -- that a witness absolutely needs to be here for cross-examination for that purpose on the 11th.

And so, first of all, I would just ask that Mr. Mangum tell us does he want every one of those declarants there in advance because we have plane tickets. As you've seen, we have people from all over the country who are -- have submitted declarations. So, first of all, if there's someone that he does not want to be present to let us know in advance would be (A) very helpful, and (B), because of these people coming from all over the country, there might have to be some issue around taking out of order, which would lead me to my next question about how you'd like to structure openings, witnesses, and then closings and your thoughts there.

MR. MANGUM: Your Honor, I guess my point on all this, and I'm sure we're in agreement, is we have a very limited amount of time, and all either of us are interested

in, of course, is being helpful to the court. And, you know, frankly it seems to me that there is a hierarchy of issues here, some of which are going to be more important to the Court, some of which, frankly, are matters for Congress, and that what we ought to do is make sure that we're spending our time and the Court's time on things that are important to the Court. In terms of making a record, people can do that with their declarations.

But I would think that what we would want to do is with input from the Court, identify what are the issues that are of most concern for the Court and focus on those, and we can leave other issues to just declarations or whatever else. And I know that's perhaps difficult because we haven't submitted our responsive papers yet. And so, you know, some of those -- some of those areas are obvious to me, others it might be. And I don't know what the Court's schedule is, but I don't know whether it would make sense that after we've filed our papers whether there's a half hour period during the week of labor day where we could just come down to the court and say, all right, let's identify the issues that are important for the court and then what the Court wants us to focus our time on, let's bring the witnesses, if any, that are pertinent to those issues and everybody else can stay home.

The Court: This is an unusual motion in many respects. It's not unusual insofar as motions for preliminary

injunctive relief. We've seen that many times before. But it is an unusually complex subject matter factually and legally. My instinct is that most of the time during our hearing will be devoted to legal argument about the implications of the rulings that precede our case and some argument about the facts.

I don't see that there's actually a great deal -- there are disputes about terms and their application and what they mean. I don't -- I don't perceive that there's really a great deal of debate amongst the parties about the scientific principles that apply, and so I'm not sure that we'll end up having much by way of live testimony and examination.

Maybe it makes the most sense to meet and talk again after we receive the reply. On the other hand, I'm mindful that it's the Plaintiffs' motion and it's your burden, and I think that you need to be given some leave to put on the case that you think you need to put on and meet your -- well, your legal and evidentiary burdens. And my -- I don't know how much guidance I can give you. I mean I think maybe the time would be best spent between the two of you deciding what issues and areas are genuinely in dispute, and you may not agree about that.

But I don't want to have 20 witnesses in the courtroom who have taken time out of their busy schedules to go to Utah to sit in on an excruciating hearing and then turn around and

fly home. That's not helpful, is it?

MR. GAEDE: No. I appreciate that. I appreciate that guidance. Also, I would say though, I do think that there is another all important aspect to the case, and that is also the 102, 103 issues that we raise. And so I agree with you on the 101 issues there's going to need to be extensive discussion around the Mayo and the Myriad decisions and the record that exists there, but I also think there's also in our view very compelling 102 and 103 issues that we have brought forward. I assume Mr. Mangum will provide some rebuttal to that, and I do think the Court is going to have to grapple with those issues as well.

THE COURT: Well, what I'm going to propose is that -- I can't recall now, Mr. Mangum. We gave you an extension of time to file your reply.

MR. MANGUM: A week from today.

THE COURT: A week from today.

MR. MANGUM: And then two weeks from today for their rebuttal declarations, but I would think that in between those times, if there were a moment to be with the Court where we have talked beforehand, that would be very, very helpful, and I'm thinking 30 minutes.

THE COURT: Well, I will make myself available whenever we need to meet, if we need to meet. What I was going to suggest is a meet and confer between counsel after

Myriad tenders its reply, give the defendants a chance to digest it a bit, discuss about -- discuss amongst yourselves the ramifications and whether there's some agreement about a course to pursue for our hearing. And if there's not, maybe identify those issues you'd like some guidance from the Court, and then notify my case administrator and we'll have you in and we'll chat if we need to do that.

MR. GAEDE: That's fine, Your Honor.

MR. MANGUM: Thank you, Your Honor.

THE COURT: All right. Is there anything else we should touch on? I don't think there are outstanding substantive issues. There were some motions for admission pro hac vice and things but I don't think anything significant.

MR. MANGUM: We're approaching entry number 100 already.

The Court: We're all very excited about that. Is there -- I am wondering about one thing, and it's just -- I guess I'm just trying to think of efficiencies. We have not consolidated these cases. We spoke briefly about this at the hearing with Gene By Gene. And I think there's reasons that -- well, these cases will not be consolidated for trial, of course, but I'm beginning to wonder -- we're making separate entries in two different cases as we're proceeding. I'm wondering if there's any reason not to consolidate the cases for the time being. I think everyone anticipated we

would act that way at least through the hearing. And then we'll have scheduling orders that will be forthcoming. It seems to me discovery should move in parallel tracks, and I can't think of any reason why we wouldn't consolidate the cases for those purposes. And then maybe by the time we get to expert discovery maybe we need to split them out or maybe not, but just to streamline the proceedings so everybody is not making two separate filings. What's your view about that, counsel?

MR. MANGUM: We're in agreement with that, Your Honor. We think the cases should be consolidated for discovery purposes.

MR. GAEDE: You know, Your Honor, I need to speak with both my clients. I know they're in firm agreement for consolidation through the P.I. No issue on that. But I do need to speak to both of them about that issue, if the Court's indulgence as to whether it should be consolidated for purposes of discovery.

THE COURT: All right. Well, that's fair enough. Of course we want you to have a chance to consult with your clients. I'm going to treat this as a stipulation to consolidation until the Court resolves the preliminary injunction issues.

And then, Mr. Gaede, if your clients wish to separate the cases out again, I'll ask you to make a motion at that time.

But we'll consolidate the 403 matter into the earlier filed matter, the 640 matter for now.

MR. GAEDE: My secretary will be thankful.

THE COURT: Everyone will I think. All right. Is there anything else, counsel, we should take up while we're here?

MR. MANGUM: No thank You.

THE COURT: I'd like to express my appreciation to all of you and your clients for the hard work you put in for preparing the materials for the Court. It was helpful and it was informative and I appreciate it. So I hope you all have a nice weekend. We'll be in recess.

(Hearing concluded 4:51 PM)

* * *

Certificate of Reporter

I, Raymond P. Fenlon, Official Court Reporter for the United States District Court, District of Utah, do hereby certify that I reported in my official capacity, the proceedings had upon the hearing in the case of University of Utah Research Foundation, et al. Vs. Ambry Genetics Corporation, case No. 2:13-CV-640RJS, in said court, on the 23rd day of August, 2013.

I further certify that the foregoing pages constitute the official Transcript of said proceedings as taken from my machine shorthand notes.

In witness whereof, I have hereto subscribed my name this 30th day of August, 2013.

/s/ Raymond P. Fenlon